Anti-trypanosomatid drug discovery

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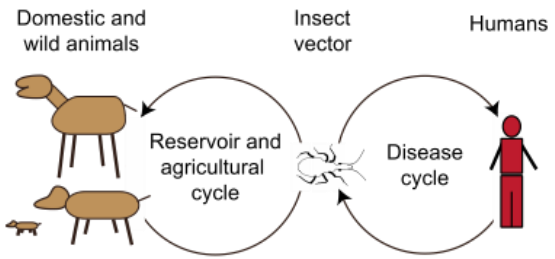
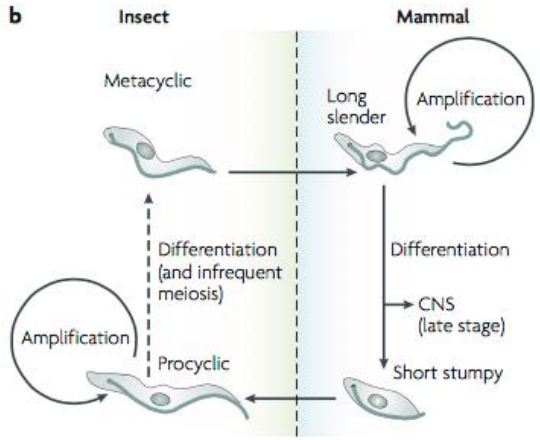
Figure for Box 1

a

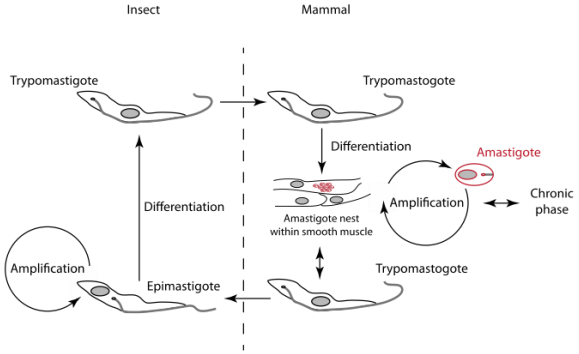


Trypanosoma brucei



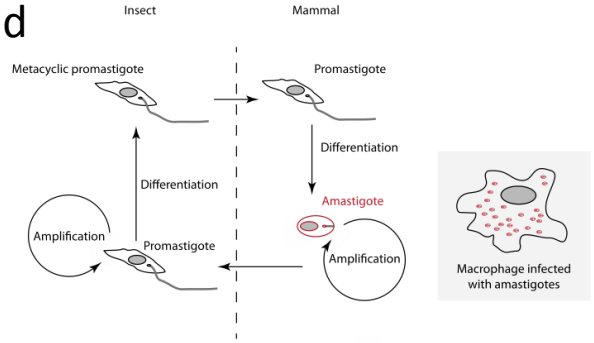
Trypanosoma cruzi

c



Leishmania

d



Compound structures for Table 1

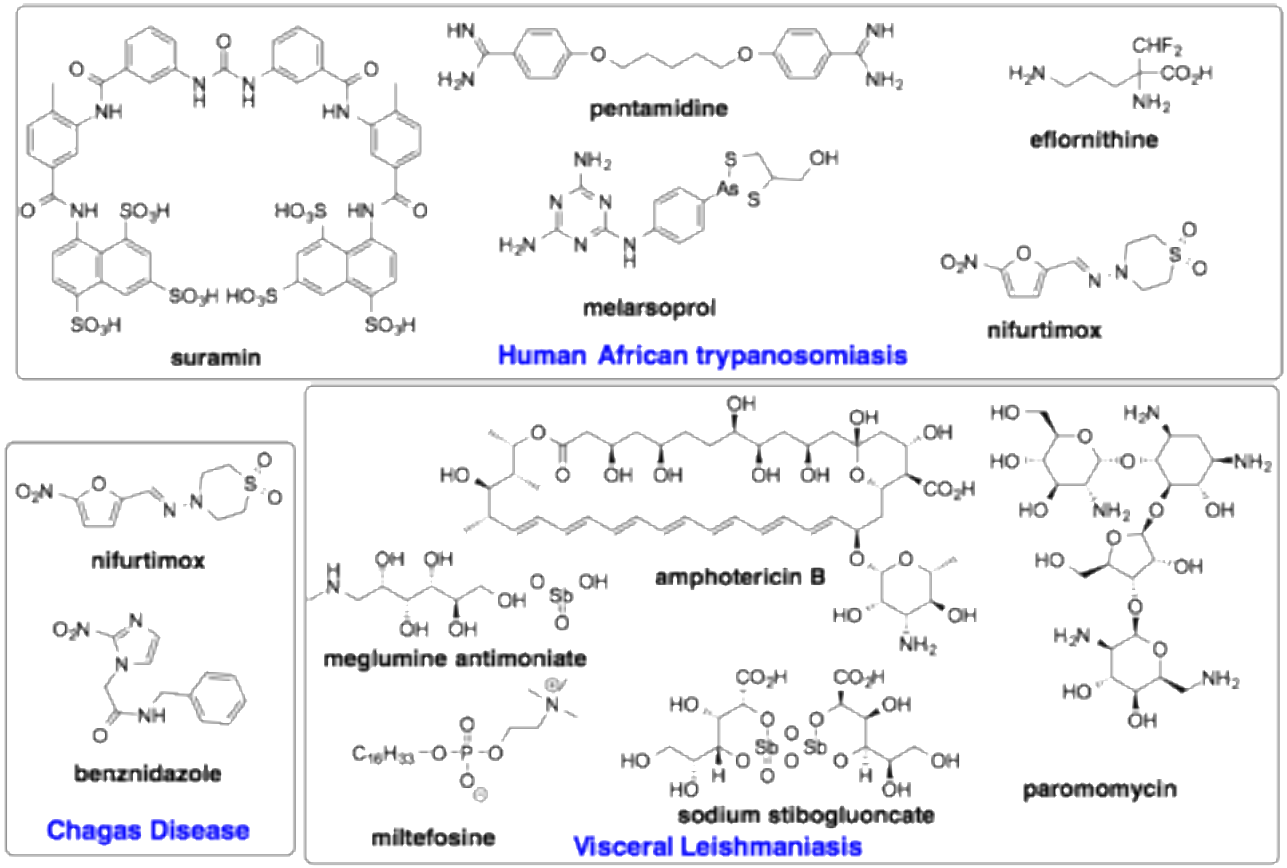


Figure 1

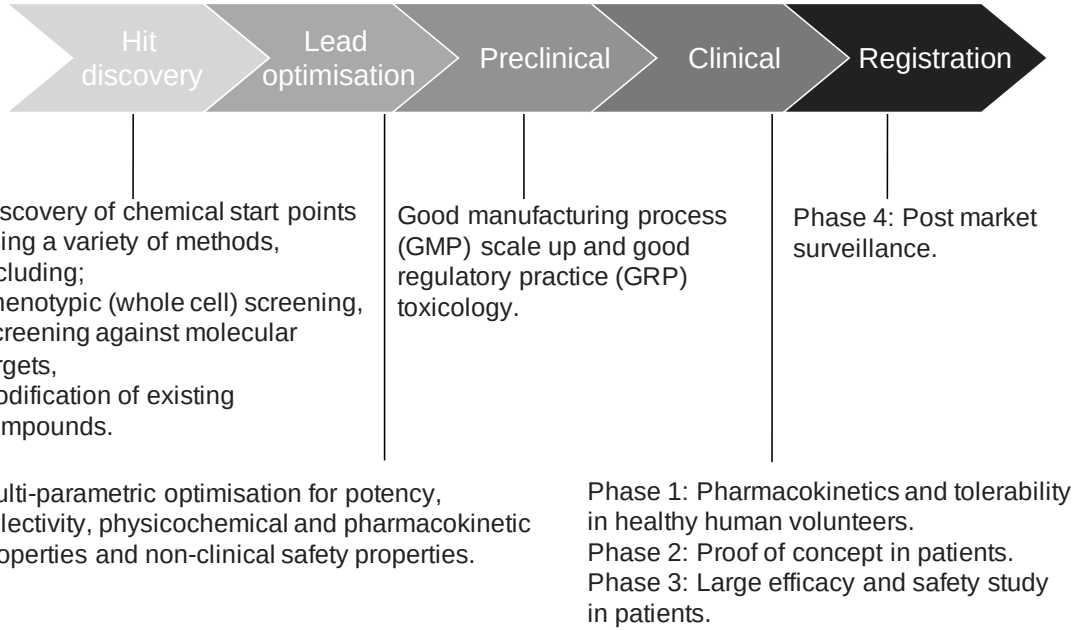
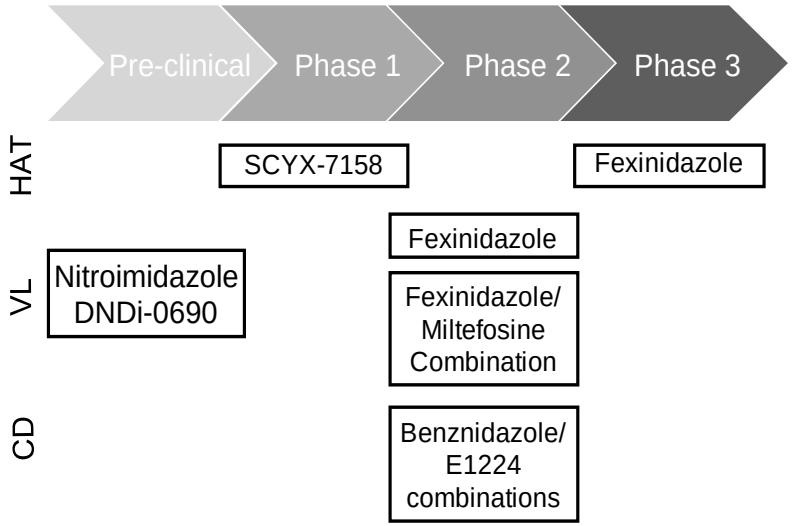
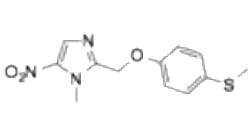
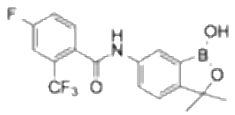

Hit discovery
Lead optimisation
Preclinical
Clinical
Registration
Discovery of chemical start points using a variety of methods, including;
Phenotypic (whole cell) screening,
Screening against molecular targets,
Modification of existing compounds.
Multi-parametric optimisation for potency, selectivity, physicochemical and pharmacokinetic properties and non-clinical safety properties.
Good manufacturing process (GMP) scale up and good regulatory practice (GRP) toxicology.
Phase 1: Pharmacokinetics and tolerability in healthy human volunteers.
Phase 2: Proof of concept in patients.
Phase 3: Large efficacy and safety study in patients.
Phase 4: Post market surveillance.

Figure 2

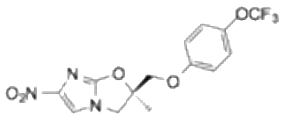




fexinidazole



SCYX-7158



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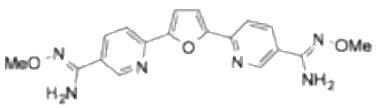
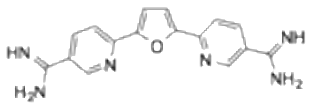
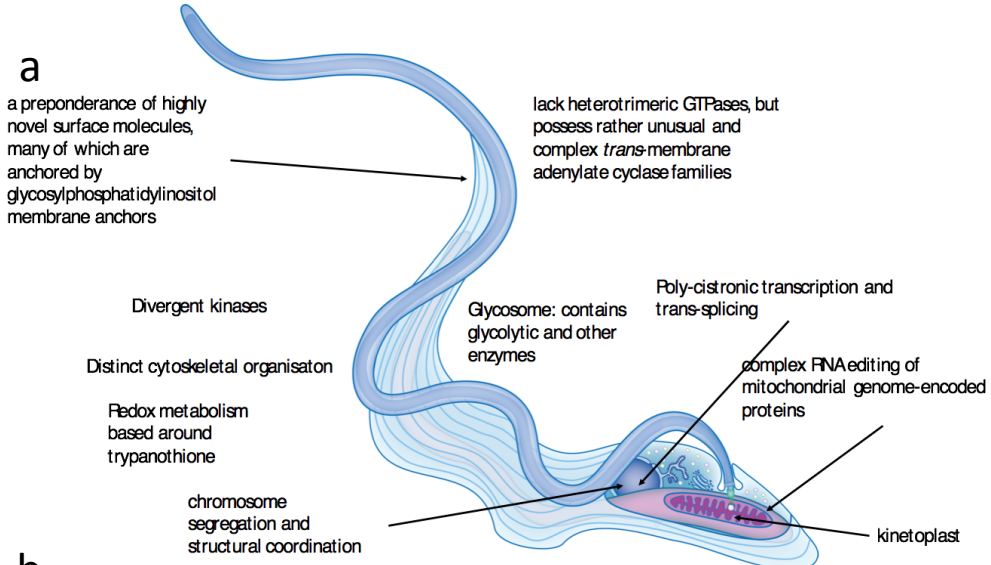


pafuramidine



DB75

Figure 3


a
a preponderance of highly novel surface molecules, many of which are anchored by glycosylphosphatidylinositol membrane anchors
lack heterotrimeric GTPases, but possess rather unusual and complex *trans*-membrane adenylate cyclase families
Divergent kinases
Distinct cytoskeletal organisaton
Redox metabolism based around trypanothione
Glycosome: contains glycolytic and other enzymes
Poly-cistronic transcription and trans-splicing
complex RNA editing of mitochondrial genome-encoded proteins
chromosome segregation and structural coordination
kinetoplast

b

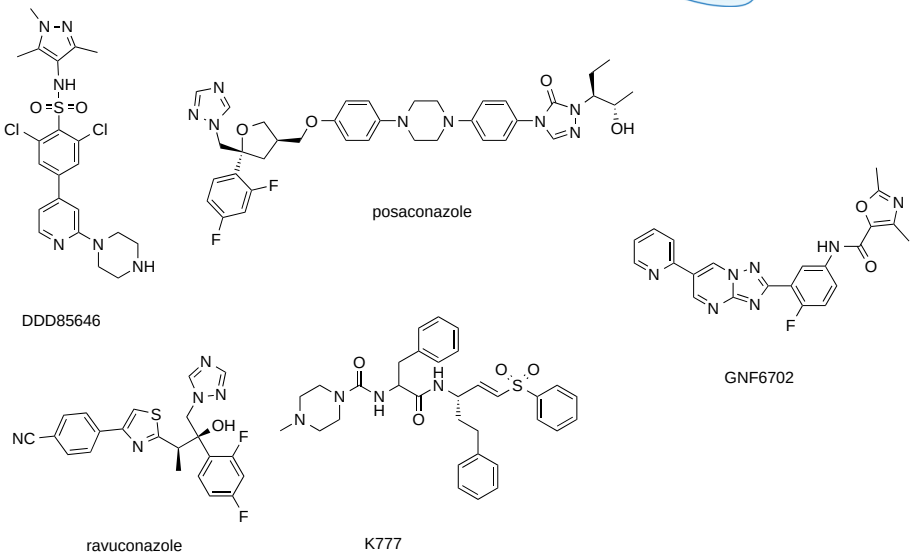
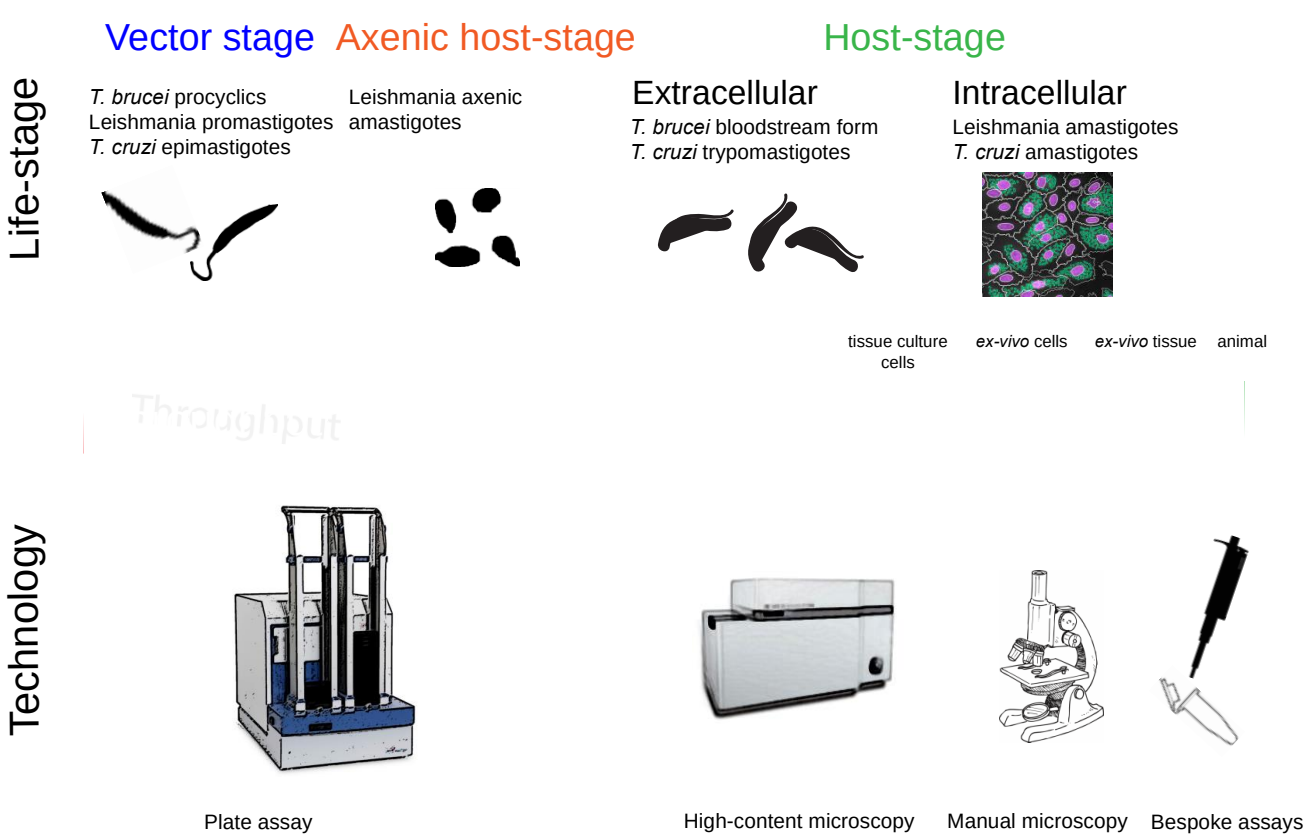

DDD85646
posaconazole
GNF6702
ravuconazole
K777

Figure 4


Vector stage
Axenic host-stage
Host-stage
Life-stage
T. brucei procyclics
Leishmania promastigotes
T. cruzi epimastigotes
Leishmania axenic amastigotes
Extracellular
T. brucei bloodstream form
T. cruzi trypomastigotes
Intracellular
Leishmania amastigotes
T. cruzi amastigotes
tissue culture cells
ex-vivo cells
ex-vivo tissue
animal
Throughput
Technology
Plate assay
High-content microscopy
Manual microscopy
Bespoke assays
Pros
Easy to handle
High-throughput
Low hazard
Easy to handle
High-throughput
Physiological relevance
Medium-throughput possible through high-content screening
Host-cell mammalian toxicity read-out
Cons
Low physiological relevance
Physiological relevance unclear
Complexity, specialist equipment and expertise required
Throughput limitations
Increased safety requirements